

Trends, risk factors, and outcomes of post-operative stroke after heart transplantation: an analysis of the UNOS database

Paulino Alvarez¹, Takeshi Kitai², Toshihiro Okamoto³, Hiromichi Niikawa⁴, Kenneth R. McCurry³, Adamantia Papamichail⁵, Ilias Doulamis⁶ and Alexandros Briasoulis^{5,7*}

¹Division of Cardiology, Heart and Vascular Institute, Cleveland Clinic, Cleveland, OH, USA; ²Department of Cardiovascular Medicine, Kobe City Medical Center General Hospital, Kobe, Japan; ³Department of Thoracic and Cardiovascular Surgery, Cleveland Clinic, Cleveland, OH, USA; ⁴Department of Thoracic and Cardiovascular Surgery, Tohoku University, Sendai, Japan; ⁵National Kapodistrian University of Athens Medical School, Athens, Greece; ⁶Department of Cardiac Surgery, Boston's Children Hospital, Harvard Medical School, Boston, MA, USA; and ⁷Division of Cardiovascular Medicine, Section of Heart Failure and Transplantation, University of Iowa, 200 Hawkins Dr, Iowa City, IA 52242, USA

Abstract

Background Post-operative stroke increases morbidity and mortality after cardiac surgery. Data on characteristics and outcomes of stroke after heart transplantation (HTx) are limited.

Methods and results We conducted a retrospective analysis of the United Network for Organ Sharing (UNOS) database from 2009 to 2020 to identify adults who developed stroke after orthotopic HTx. Heart transplant recipients were divided according to the presence or absence of post-operative stroke. The primary endpoint was all-cause mortality. A total of 25 015 HT recipients were analysed, including 719 (2.9%) patients who suffered a post-operative stroke. The stroke rates increased from 2.1% in 2009 to 3.7% in 2019, and the risk of stroke was higher after the implantation of the new allocation system [odds ratio 1.29, 95% confidence intervals (CI) 1.06–1.56, $P = 0.01$]. HTx recipients with post-operative stroke were older ($P = 0.008$), with higher rates of prior cerebrovascular accident (CVA) ($P = 0.004$), prior cardiac surgery ($P < 0.001$), longer waitlist time ($P = 0.04$), higher rates of extracorporeal membrane oxygenation (ECMO) support ($P < 0.001$), left ventricular assist devices (LVADs) ($P < 0.001$), mechanical ventilation ($P = 0.003$), and longer ischaemic time ($P < 0.001$). After multivariable adjustment for recipient and donor characteristics, age, prior cardiac surgery, CVA, support with LVAD, ECMO, ischaemic time, and mechanical ventilation at the time of HTx were independent predictors of post-operative stroke. Stroke was associated with increased risk of 30 day and all-cause mortality (hazard ratio 1.49, 95% CI 1.12–1.99, $P = 0.007$).

Conclusions Post-operative stroke after HTx is infrequent but associated with higher mortality. Redo sternotomy, LVAD, and ECMO support at HTx are among the risk factors identified.

Keywords Post-operative stroke; Heart transplantation; Mortality

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*Correspondence to: Alexandros Briasoulis, Division of Cardiovascular Medicine, Section of Heart Failure and Transplantation, University of Iowa, 200 Hawkins Dr, Iowa City, IA 52242, USA. Tel: 319-678-8418; Fax: 319-353-6343. Email: alexbriasoulis@gmail.com

Introduction

Heart transplantation (HTx) continues to be standard of care for selected patients with advanced heart failure with a 1 year survival of approximately 90%.^{1,2} Primary graft failure and infection are the most prevalent causes of death in the first 30 days and 1 year, respectively.³ Advances in clinical

management, organ selection and preservation, desensitization protocols, and changes in allocation policies continue to improve heart transplant recipients' survival and quality of life.⁴

Patients undergoing HTx have a lower risk of stroke than patients with heart failure on the waiting list.⁵ However, HTx has been associated with a higher risk of stroke than other

cardiac surgery types, with stroke incidence between 5% and 11%. Approximately 20% will occur within 2 weeks after HTx.^{6–8} Zierer *et al.* identified advanced age, preoperative left ventricular assist device (LVAD) support, preoperative intra-aortic balloon pump (IABP), prolonged cardiopulmonary bypass, and post-operative hepatic failure as independent predictors of early neurologic complications.⁹ Early stroke after HTx has been associated with decreased long-term survival in children.¹⁰ A higher proportion of cryptogenic stroke and unusual stroke causes have been reported in HTx recipients.¹¹ A recent analysis of the Scientific Registry of Transplant Recipients database did not identify stroke as a significant factor related to early, constant, or late mortality risk.¹²

In October 2018, a six-tier heart transplant allocation system replaced the three-tier system in the USA.¹³ We would highlight two of those changes. First, the Status 1 of the old system was divided into three statuses: Status 1 [extracorporeal membrane oxygenation (ECMO), nondischageable biventricular assist devices, and mechanical circulatory support (MCS) devices with ventricular tachycardia], Status 2 (IABP, percutaneous ventricular assist devices, surgical nondischageable LVAD, total artificial heart, MCS with device failure and ventricular tachycardia, or fibrillation), and Status 3 (LVAD 30 days, high dose or >1 inotrope, Statuses 1 and 2 after 14 days, and MCS with other complications). Second, the organ distribution area was expanded to 500 nautical miles from the transplant centre for Status 1 and 2 patients. Studies analysing the impact of the new allocation system have reported a significant increase in preoperative MCS (e. g. IABP: 7.6% → 26.2%; ECMO: 1.4% → 5.1%), increased ischaemic time, and a decrease in waitlist mortality, and some reports increased post-transplant mortality, but this has not been consistent.^{14–18}

The information about the incidence of post-operative stroke in the current era and the potential impact of the new allocation system is scarce.¹⁹ To address this knowledge gap, we performed an analysis of the United Network for Organ Sharing (UNOS) database to investigate the trends, risk factors, and prognostic implications of post-operative stroke in heart transplant recipients.

Methods

Data source

We analysed the UNOS database from the thoracic organ transplant registry from 2009 to 2019, with follow-up through January 2020. The data include all patients undergoing thoracic organ transplantation in the USA. The registry records additional clinical information at the time of transplant, such as perioperative events, and continues to follow the recipient after transplant.

Study design and patient population

All first-time HTx recipients who were 18 years old or older were included. Patients who received a multiorgan transplant or in whom post-operative stroke information was missing were excluded. Patients were primarily stratified by the presence or absence of post-operative stroke as documented in the UNOS database.

Outcomes

Baseline characteristics and risk factors for post-operative stroke were analysed. The primary outcome was all-cause mortality.

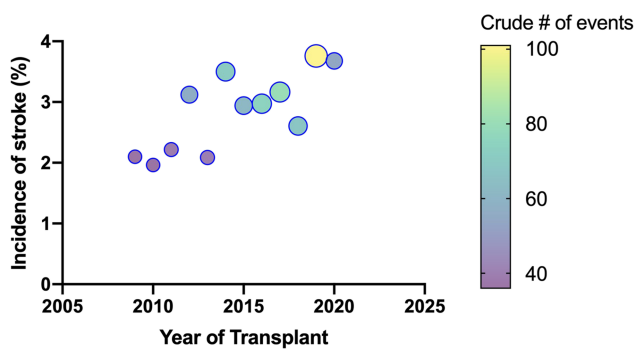
Statistical analysis

We compared baseline characteristics between study groups using χ^2 test for categorical variables and the independent-sample *t*-test or Wilcoxon rank-sum test (as appropriate) for continuous variables. Risk factors for post-operative stroke identified in univariate analysis with $P < 0.05$ were included in the multivariable logistic regression model. Mortality was assessed for all risk factors, including post-operative stroke, in a univariate model. Significant risk factors (donor and recipient characteristics) were then analysed with a multivariable analysis using the Cox proportional hazard regression model. Survival was analysed using the Kaplan–Meier method with statistical differences between survival curves assessed using the Mantel–Cox log-rank test. In addition, modelling based on 30 day landmark analysis was performed to assess long-term survival independent of early mortality. To evaluate the interaction the heart allocation policies, we assessed the incidence of stroke before and after October 2018 and the associated survival. Variables with more than 10% missing data were excluded from the multivariable model. All statistical tests were two-sided, and $P < 0.05$ was considered to indicate statistical significance. Analyses were performed using Stata software, Version 16 (StataCorp LLC).

Results

We identified 28 385 adult patients (18 years or older) who underwent HTx during the study period. After excluding patients who had multiorgan transplantation ($n = 2112$) or whose stroke information was missing ($n = 1258$), a total of 25 015 patients were included in the study. Of the 25 015 patients, 719 patients (2.9%) had a post-operative stroke. The prevalence of stroke ranged from 1.9% in 2010 to 3.76% in 2019. The trends in post-operative stroke during the study period are shown in *Figure 1*.

Figure 1 Trends in post-operative stroke incidence after heart transplantation.



Heart transplantation recipients with post-operative stroke were older ($P = 0.008$), with higher rates of prior cerebrovascular accident (CVA) ($P = 0.004$), prior cardiac surgery ($P < 0.001$), longer waitlist time ($P = 0.04$), higher rates of ECMO support ($P < 0.001$), LVADs ($P < 0.001$), mechanical ventilation ($P = 0.003$), and longer ischaemic time ($P < 0.001$) (Table 1). After multivariable adjustment for recipient and donor characteristics listed in Table 1, age, prior cardiac surgery, CVA, support with LVAD, ECMO, ischaemic time, and mechanical ventilation at the time of HTx were independent predictors of post-operative stroke (Figure 2).

Patients with stroke had higher rates of haemodialysis after HTx (37% vs. 11% among those without stroke, $P < 0.001$) and blood transfusion (31% vs. 22% among those without stroke, $P < 0.001$). Three hundred forty-two patients with stroke died (47.6%) compared with 4657 patients without stroke (19.2%). Among those with stroke, 148 patients died within the first 30 days after HTx (43.3% of deaths vs. 15.2% among those without stroke). Stroke was associated with increased risk of 30 day [odds ratio 4.44, 95% confidence intervals (CI) 3.52–5.60, $P < 0.001$] and all-cause mortality after HT after multivariable adjustment [hazard ratio (HR) 1.49, 95% CI 1.12–1.99, $P = 0.007$] (Figure 3A and 3B). Overall, the 30 day landmark survival was significantly lower in patients with stroke after adjustment for the recipient and donor characteristics (HR 1.4, 95% CI 1.1–1.9, $P = 0.017$).

A total of 3598 patients analysed in the new allocation system of those 127 had a post-operative stroke. Notably, the ischaemic time was significantly higher in the new allocation system (new 3.43 ± 1.03 h vs. old 3.15 ± 1.05 , $P < 0.0001$). The risk of stroke was higher after implementing the new allocation system (odds ratio 1.29, 95% CI 1.06–1.56, $P = 0.01$).

Discussion

The salient findings of this retrospective analysis of heart transplant recipients with and without post-operative stroke

from a nationwide representative database from 2009 to 2020 can be summarized as follows: (i) the incidence of post-operative stroke is 2.9% after HTx; (ii) the incidence of stroke has increased during the study period; (iii) prior cardiac surgery, longer ischaemic time, LVAD, and ECMO support at HTx are risk factors for stroke; (iv) HTx recipients with stroke had higher rates of mechanical ventilation and need for dialysis and blood transfusion; (v) post-operative stroke is an independent predictor of all-cause mortality after HTx; and (vi) the risk of stroke was higher after implementation of the new allocation system.

Stroke and encephalopathy are the most frequent neurologic complications after cardiac surgery. The incidence of stroke depends on the complexity and number of cardiac procedures performed and has declined after coronary artery bypass graft surgery despite an increasing patient risk profile.²⁰ Most strokes occur post-operatively in the first 2 days after cardiac surgery, while at least one-third of strokes occur intraoperatively,²⁰ with an increased risk of stroke persisting up to 2 years after surgery.²¹ However, it is important to note that in analyses of large databases, only clinical stroke is reported as the incidence of 'silent' stroke uncovered by neuroimaging is estimated to be much higher.²² Similarly, in our study, the stroke incidence is comparable with that reported among patients who underwent combined valvular and coronary artery bypass graft surgery.²³ Still, it is possible that due to lack of neuroimaging data, the rates of subclinical stroke are much higher.

Regarding risk factors related to post-operative stroke, advanced age, prior stroke, atherosclerosis of the ascending aorta, carotid arteries, renal failure, diabetes, left ventricular dysfunction, and operative parameters related to the complexity of the surgery and cardiopulmonary bypass are commonly identified in large cohort analyses.^{20–23} In our study, patients with post-operative stroke tended to be overall 'sicker' with higher rates of prior cardiac surgery, need for ECMO support, and use of LVAD at the time of HT. Furthermore, patients with stroke developed additional complications such as need for dialysis and bleeding requiring blood transfusions more frequently than those without stroke. Although this large registry data do not elucidate mechanisms responsible for post-operative stroke, various causes such as cerebral hypoperfusion from intraoperative hypotension or diminished cardiac output, athero-, thrombo-, or air-embolization due to manipulation of the aorta and cardioembolic due to atrial fibrillation are responsible for these events. Patients with LVAD usually have longer operative and cardiopulmonary bypass time due to the operative complexity related to prior sternotomy and device explantation. These unique operative challenges may increase the risk of stroke due to intraoperative hypotension and embolization and translate into higher rates of complications after HTx.²⁴ Also, the increasing utilization of LVADs as a bridge to transplantation in the past decade may explain the increasing trend in

Table 1 Baseline characteristics among patients with and without stroke after heart transplantation

Variable	Without post-operative stroke (n = 24 296)	With post-operative stroke (n = 719)	P-value
<i>Recipient characteristics</i>			
Age at transplantation, years (SD)	53 (13)	54 (12)	0.008
Ethnicity			
White (%)	15 947 (66)	490 (68)	0.364
Black (%)	5238 (22)	136 (19)	
Other (%)	3111 (13)	103 (14)	
BMI at listing, kg/m ² (SD)	27 (5)	27 (5)	0.869
Female gender (%)	6401 (26)	189 (26)	0.972
ABO blood group			
O (%)	9495 (39)	283 (39)	0.284
A (%)	9764 (40)	309 (43)	
B (%)	3648 (15)	100 (14)	
AB (%)	1389 (57)	27 (4)	
Diabetes (%)	6773 (28)	208 (29)	0.682
Smoking (%)	11 235 (46)	333 (46)	0.962
Prior CVA (%)	1441 (6)	61 (9)	0.004
Ischaemic time, h (SD)	3.18 (1.05)	3.36 (1.18)	<0.001
Prior cardiac surgery (%)	9594 (40)	365 (52)	<0.001
Creatinine, mg/dL (SD)	1.2 (0.5)	1.2 (0.5)	0.153
Albumin, mg/dL (SD)	3.7 (0.7)	3.7 (0.7)	0.215
Implantable defibrillator (%)	18 922 (79)	521 (74)	0.002
Days on Status 1a (SD)	30 (58)	33 (61)	0.129
Total days on waitlist (SD)	225 (367)	253 (423)	0.044
Inotropes at transplant (%)	9008 (37)	201 (28)	<0.001
IABP at transplant (%)	2499 (10)	67 (9)	0.4
VAD type at transplant (%)			
None (%)	13 443 (55)	275 (38)	<0.001
LVAD (%)	10 067 (41)	395 (55)	
RVAD (%)	46 (0.2)	3 (0.4)	
TAH (%)	241 (0.9)	19 (3)	
LVAD + RVAD (%)	498 (2)	27 (4)	
ECMO at transplant (%)	314 (1)	29 (4)	<0.001
Mechanical ventilation at transplant (%)	315 (1)	27 (4)	<0.001
Acute rejection (%)	2121 (9)	55 (8)	0.448
Post-transplant dialysis (%)	2572 (11)	262 (37)	<0.001
Post-transplant pacemaker (%)	701 (3)	30 (4)	0.04
Need for blood transfusion (%)	5238 (22)	217 (31)	<0.001
<i>Donor characteristics</i>			
Donor age (SD)	32 (11)	33 (12)	0.112
Donor ethnicity			
White (%)	15 618 (64)	455 (63)	0.904
Black (%)	3952 (16)	120 (17)	
Other (%)	4726 (19)	144 (20)	
Donor ABO			
O (%)	12 243 (50)	365 (51)	0.198
A (%)	8770 (36)	266 (37)	
B (%)	2718 (11)	80 (11)	
AB (%)	565 (2)	8 (1)	
Donor female gender (%)	7186 (30)	195 (27)	0.155
Donor BUN, mg/dL (SD)	22 (18)	22 (17)	0.857
Donor creatinine, mg/dL (SD)	1.5 (1.5)	1.5 (1.4)	0.887
Donor SGOT, mg/dL (SD)	105 (317)	113 (374)	0.493
Donor SGPT, mg/dL (SD)	114 (436)	105 (241)	0.569
Donor total bilirubin, mg/dL (SD)	1.1 (1.4)	1.1 (1.7)	0.353
Donor diabetes (%)	6773 (28)	208 (29)	0.682
Donor BMI, kg/m ²	28 (6)	28 (7)	0.047

BMI, body mass index; ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; RVAD, right ventricular support device; SD, standard deviation; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; TAH, total artificial heart. P-values in bold are statistically significant.

post-operative stroke after HT. In our analysis, HTx recipients with stroke had longer ischaemic time, which further increased in this population after implementing the new allocation system and may explain the higher rates of stroke. With regard to atrial fibrillation, the frequency of this

early after surgery is lower compared with its incidence post-pericardiectomy in the setting of other cardiac surgeries, and this is likely due to surgical pulmonary vein isolation and cardiac denervation that occur with HT in addition to the frequent use of amiodarone among the heart failure population

Figure 2 Forest plot depicting the risk factor for post-operative stroke after multivariable adjustment for donor and recipient characteristics. ECMO, extracorporeal membrane oxygenation; ICD, implantable cardioverter defibrillator; LVAD, left ventricular assist device.

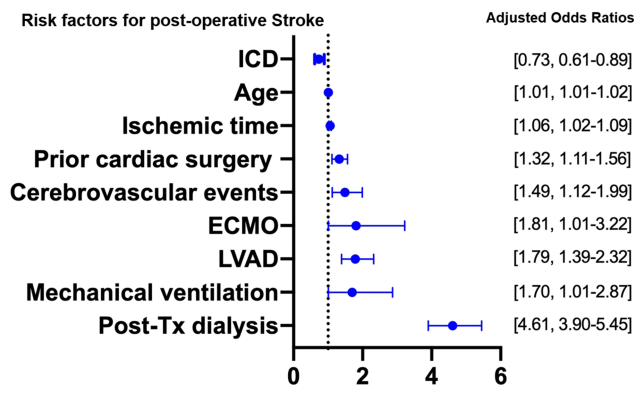
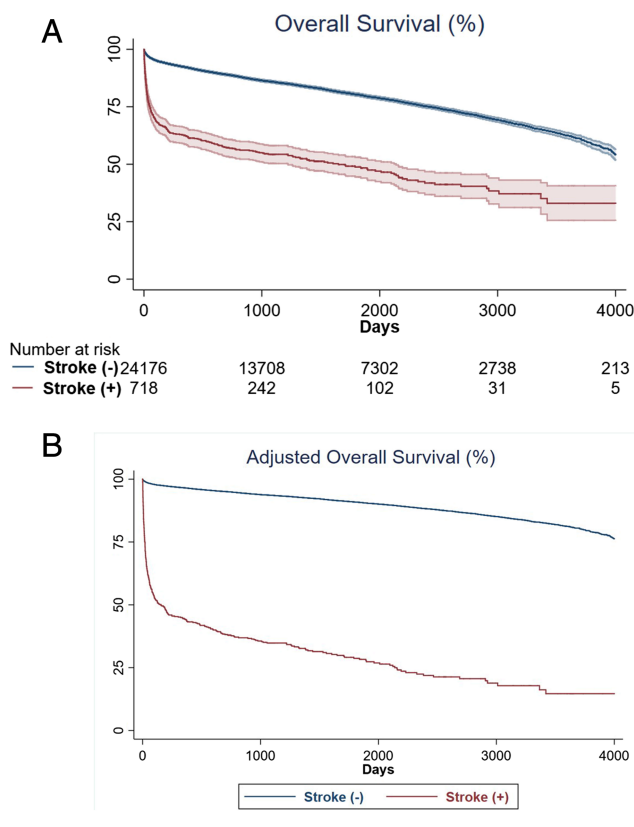


Figure 3 Kaplan–Meier curves of (A) overall survival and (B) adjusted overall survival after heart transplantation.



before HTx.²⁵ Lastly, the higher risk of stroke seen in the era after the implementation of the new allocation in October 2018 is concerning. Among the risk factors for post-operative stroke, ECMO and ischaemic time are increasing since the implementation of the new allocation

system.^{14,15,26} Stroke affects approximately 4% of patients with venoarterial ECMO, and the cause is multifactorial.²⁷ Careful monitoring of neurological status, anticoagulation management, and left ventricular venting strategies may mitigate complications.²⁸ Alternative percutaneous transvalvular or surgical biventricular MCS can be considered.^{29,30} The use of *ex vivo* perfusion technologies may modulate the risk associated with prolonged ischaemic time such as stroke.³¹ The FDA approved an Organ Care System for clinical use, and post-approval monitoring would help to evaluate the impact of *ex vivo* perfusion in post-operative stroke.³² More data need to be accumulated before safe conclusions about the characteristics of HTx recipients and their impact on post-operative complications and mortality in the current allocation system can be reached.

The interpretation of the findings presented here should be performed in light of specific limitations inherent to the source of data and study design. First, this was a retrospective analysis of the UNOS database, and analysis is constrained to available information in the dataset. Information about the timing, type, radiographic, and clinical severity of these events is lacking. Therefore, we cannot determine post-operative stroke's impact on the quality of life, functional status, recurrent stroke risk, and overall mortality. Second, the observational nature of the analysis implies that the effect of the changes in allocation policy reported represents an association only, and a causal effect cannot be determined. Although we adjusted for multiple confounding factors, the possibility of residual confounding cannot be eliminated. Third, only limited data are available after the most recent policy change in 2018; hence, this policy change's long-term impact is yet to be determined. Our study's main strength is that UNOS is a clinical database currently used broadly for epidemiologic analysis and outcomes with data reflecting current practices in the USA.

In conclusion, post-operative stroke after HTx is uncommon, but it is accompanied by a considerable impact on mortality. Its incidence has increased and occurs with other serious complications, particularly in patients requiring MCS with LVADs or ECMO. Given the overall improving outcomes after HTx, it is crucial to focus on early identification and prevention of often disabling complications such as stroke. Approaches to decrease ischaemic time, especially after implementing the new allocation system, may reduce stroke rates. Future studies should investigate the mechanisms, timing, and imaging characteristics of post-operative stroke and examine its effects on long-term cognitive function, functional status, and heart transplant patients' quality of life.

Conflict of interest

No conflict of interest declared.

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